ORIGINAL ARTICLE

A COMPARISON OF DRUG RESISTANCE PATTERN IN CATEGORY-I FAILURE VERSUS CATEGORY-I RELAPSE PULMONARY TB PATIENTS ATTENDING A TERTIARY CARE HOSPITAL IN SOUTH PUNJAB, PAKISTAN.
IS WHO CATEGORY-II ATT REGIMEN APPROPRIATE?

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ABSTRACT:

Introduction: There are emerging reports of increasing number of patients with drug resistant tuberculosis in WHO category-ll patients (Category-l failure and Category-l relapse groups). Therefore, current WHO recommendation for the treatment of Category-ll patients may not be the best option. We conducted a prospective study in which drugs sensitivity pattern in patients in Category-l failure and relapse were performed at the start of treatment and compared**.**

Setting: The study was done in the chest clinic of a tertiary care hospital (Nishtar Medical Institution Multan, South Punjab) and an attached DOTS TB center. MTB cultures and DST was done at Aga Khan University Hospital TB laboratory at Karachi which is an accredited reference laboratory for this test.

Objective: To determine the pattern of drug resistance in category-I failure and relapse pulmonary TB patients and also to see if the currently recommended WHO Category-II regimen is appropriate for these two groups.

Design: This was a prospective, analytic study. A total of 88 pulmonary tuberculosis patients who had taken anti-tuberculosis treatment were evaluated prospectively with respect to their drug resistance pattern by sputum culture for acid-fast bacilli (AFB) and sensitivity testing with first line drugs (FLD) as well as second line drugs (SLD).

Results: A total of 88 patients were found to be evaluable; 33 (37%) were Cat-I failure and 55(63%) were Cat-I relapse. Among 33 Patients in Cat-1 failure group, 13 had taken DOTS treatment and 20 received Non-DOTS treatment. Four (12%) cases were XDR-TB, 16 (48%) were MDR-TB, 5 (15%) were Poly resistant TB, 4 (12%) were Mono resistant and 4(12%) were sensitive to all drugs. A higher percentage, 65% (13/20 cases) of MDR/XDR-TB was found in Non-DOTS group as compared to DOTS group, 35 %.(7/20 cases). Among 55 Patients in Cat-I relapse, 33 had taken DOTS treatment and 22 received Non-DOTS treatment (p=0,001) Four (7%) cases were XDR-TB, 20 (36%) were MDR-TB, 3 (5%) were Mono resistant, 3 (5%) were Poly resistant and 25 (45%) were sensitive to all drugs. A higher percentage, 55% (13/24 cases) of MDR/XDR-TB was found in DOTS group as compared to Non-DOTS group 45% i.e. 11/24 cases (p=0.006).

Conclusion: Our results suggest an urgent need to revise our management strategies for both Category-I failure and relapse patients. Early TB culture and drug sensitivity should be performed on these patients in order to avoid spread of MDR-TB and its associated morbidity and mortality, by choosing correct regimen on the basis of DST results performed in the beginning.

Key words: Multi drugs resistant tuberculosis; acquired drug resistant; extensively drug resistant tuberculosis; Pakistan, WHO TB guidelines, TB relapse.

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INTRODUCTION:

Tuberculosis is a common and deadly infectious disease caused by mycobacterium tuberculosis in humans[1]. It is among the most serious infectious causes of global morbidity and mortality[2,3]. According to WHO more than 8 million people get tuberculosis and 1.8 million die due to tuberculosis[4,5]. More than 30,000 cases of tuberculosis develop in Pakistan every year, three quarter of which is concentrated in productive age group[6].

Newly diagnosed patients of pulmonary tuberculosis are categorized as category-I patients according to WHO and National Tuberculosis Control Program (NTCP) guidelines. As per WHO/NTCP guidelines, category-I tuberculosis patients are treated with four drugs combination in intensive phase Rifampicin (R) +Isoniazid (H) +Ethambutol (E) +Pyrazinamide (Z) for two months followed by two drugs Isoniazid (H)+ Ethambutol (E) during maintenance for six months. However, in out side DOTS treatment, maintenance regimen usually consists of three drugs i.e. Rifampicin +Isoniazid +Ethambutol (RHE).

WHO category ll includes patients who continue to have active tuberculosis even after 5 months of taking category-I anti-tuberculosis treatment i-e category-I failure[6] and patients who relapse after successful completion of category-I regimen i.e. category-I relapse[6].

Success rate of Cat-1 regimen under DOTS program varies in different studies in different countries. In one study conducted in Gulabi Bagh civil clinic (India) from 1994 to 2005, failure rate of category-I was 3.4% and relapse rate was 9%[7]. Another study conducted in rural areas of Tamil Nadu between 1999 and 2002, failure rate was 5%[8]. Similarly another study conducted in central Lima (Peru) in 2009 showed failure rate of 2.9%[9].

A study in Gujarat (India) about drug resistance in previously treated TB patients showed INH resistance at 7.5% followed by Rifampicin 0.97%, Etmambutol 0.4% and Streptomycin 1.4%[10]. Similarly in another WHO study in previously treated patients, frequency of resistance to at least one drug ranged from 0 to 82%. Median prevalence of resistance to specific drugs were H 19.4%, S 11.4%, R 8.7%.E 3.5% and median prevalence of Multi Drug Resistance (MDR) was 7%.[11].

The current recommendation for treating both Category-I failure and Category -I Relapse patients is with same regimen of Category-II ($R_8H_8E_8Z_3S_2$) [12].

However, a study published in 2004 by Chiang CY, et al in Taipei has showed drug sensitivity pattern to first line anti TB drugs in two groups being different, with Category-I failure patients being resistant to higher number of drugs than Category-I relapse patients (69.7% vs33.3%) [13]. A study conducted in Central Siberian prison showed that treatment failure rate of Category-II for Category-I failure was 35% and there was high incidence of MDR-TB[14]. Another study in Vietnam showed that 80% cases of Category-I failure and 8% cases of Category-I relapse had MDR. In Category-I failure cases, half were due to acquired drug resistance.[15] A study in Lima, Peru showed that treatment of Category-I failure according to DST pattern was 5 times more likely to cure patients than Category-II only (79% vs. 15%) [16]. Similarly a study conducted in Tehran (Iran) showed that treatment success of Category-I failure according to DST pattern was high as compared to Category-II regimen only (72% vs. 50%) [17]. Commencement of Category-II

treatment with addition of a single drug (streptomycin) in both groups may result in high failure rates as various studies have shown high prevalence of multi-drug resistance (MDR) in both Category-I failure relapse patients.

We felt a need to conduct a comparative study in order to determine the pattern of drug resistance in Category-I failure and Category-I relapse patients in our tertiary care center. This will guide us to develop more appropriate guidelines for the management of these patients. Early detection of Drug Resistant TB patients will not only prevent the spread but is likely to reduce morbidity and mortality. In the long run it is likely to save money and reduce burden of MDR-TB.

STUDY POPULATION AND METHODS

Organizational and Survey outline

Survey area:

The chest clinic of the tertiary care hospital (Nishtar Medical College, Multan) and attached DOTS centre was the survey area. This study was designed to determine the drug resistance pattern of Mycobacterium Tuberculosis from sputum cultures of Cat-I failure and relapse patients attending the chest clinic and the DOTS center.

Preparatory Phase:

The investigator team comprised of doctors and laboratory staff working in the department of Pulmonology in Nishtar Hospital Multan. Team was headed by Prof. and head of department. All investigators were trained in all aspects of study including case selection, collection of sputum sample, entries to be made in relevant forms and dispatch of specimens to collection centers of central laboratory.

Data Analysis

Sampling:

This was a comparative study to estimate the drug sensitivity pattern in both groups of Tuberculosis. Patients were selected who fulfill the inclusion criteria and enrolled over period of 1 year. Sputum specimens were sent in container provided by central laboratory along with individuals forms filled out by investigator at diagnostic centre; including declaration by investigators that patient has not taken Cat-II previously. Patients were given information leaflets and asked for informed consent. In case of illiterate subjects, the information was read and explained to them and their oral consent to participation trial was requested.

Inclusion Criteria:

- Patients with Cat-I failure and relapse TB
- Patients with age > 18 years
- Patients with Pakistani Resident
- Sputum collected for culture before start of Cat-II

Exclusion Criteria:

- Category II treated patients
- PTB defaulter patients
- Pregnant ladies with pulmonary TB

Central Laboratory:

The department of microbiology laboratory at Agha Khan University Hospital was used as central laboratory for culture and DST.

Microbiology Method:

Sputum specimen collection for culture and DST:

Sputum samples were collected, stored and transported to the central laboratory using standard operating procedure (SOP).

Complete information on all samples that met the inclusion criteria were noted in full in the TB culture register. Each sample was assigned a serial number to permit proper identification of the specimen obtained from the diagnostic centre and to facilitate feedback of the culture result.

PROCESSING OF SPUTUM SPECIMEN

Microbiological methods

Specimen processing:

All samples were decontaminated with N-acetyl-L-cystein (NALC) sodium hydroxide according to the standard protocol. All specimens were concentrated by centrifugation for 30 min and sediments were used for acid-fast bacilli microscopy and culture.

Microscopy:

Smears for microscopy were screened using auramine-rhodamine staining. Positive slides were further confirmed by staining with Kinyoun modification of Ziehl-Neelsen stain.

Isolation of M. tuberculosis:

Mycobacterial cultures were performed on both liquid and solid media. Sediments were cultured at 37 ^{o}C using Lowenstein-Jensen medium and Mycobacteria Growth Indicator Tube (Becton Dickinson Diagnostic Instrument System, Sparks, MD, USA). For the LJ slant, 0.1 ml of concentrated specimen was inoculated and incubated for 8 weeks. MGIT vials were inoculated with 0.5 ml of specimen and incubated at 37^{0}C after supplementation of the medium with oleic acid-albumin-dextrose - catalase and PANTA (polymyxin B, amphotericin B, nalidixic acid, trimethoprim and azlocillin). Growth from the positive LJ slant and MGIT vials were first stained with Kinyoun. M. tuberculosis was then identified using the BACTEC NAP TB differentiation test (Becton Dickinson).

Drug susceptibility testing:

DST was done at a WHO accredited Aga Khan University Hospital which is one of the national reference laboratory. DST was performed using standard agar proportion method on enriched Middlebrook 7H10 medium (BBL, Beckton Dickson) at following drug concentrations: Rifampcin 1 and 5 ug/ml, Isoniazid 0.2 and 1 ug/ml, Streptomycin 2 ug and 10 ug/ml and Ethambutol 5 and 10 ug/ml. Disc elution susceptibility plates were prepared using paper susceptibility discs (BBL). McFarland No.1 standard suspension of isolates was made from growth on L J slant and diluted to 10^{-2} and 10^{-4}. The inoculated plates were incubated at 35^{0}C and examined for growth each week for 8 weeks. M.tuberculosis was considered resistant to a given drug when growth of > 1% above the drug free control was observed in the drug containing area. Pyrazinamide (PZA) sensitivity was carried out using BACTE 7H12 Medium, pH6.0 at 100 g/ml (BACTEC USA) in accordance with the manufacture's instructions. M. tuberculosis H37Rv was used as a control with each batch of DST.

RESULTS:

A total of 88 patients were found to be evaluable; 33 (37%) were Cat-I failure and 55(63%) were Cat-I relapse. In Cat-I failure group the strength of female was 20 and strength of male

was13 while 25 were <35 years of age. In Cat-I relapse group the strength of female was 22 and strength of male was 33 while 26 were <35 years of age.

DST IN CAT-I FAILURE GROUP

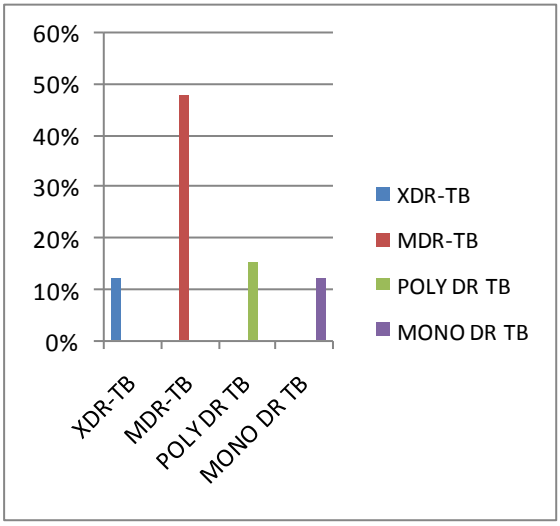
Among 33 Patients, 13 have taken DOTS treatment and 20 have taken non-DOTS treatment. 20(60%) were resistant to Rifampcin, 25 (75%) to Isoniazid, 20 (60%) to Ethambutol, 24 (72%) to Pyrazinamide, 21(63%) to Streptomycin, 19 (57%) to Quinolones (Q) and in the second line inject able amino- glycosides, 4(12%) were resistant to Kanamycin (Km), 2(6%) to Amikacin (Amk) and 2(6%) to Capreomycin (Cm).

4(12%) cases were Extensively Drug Resistant (XDR) TB, 16(48%) were MDR-TB, 5(15%) were Polyresistant TB, 4(12%) were Monoresistant and 4(12%) were sensitive to all drugs.

Table I: DST Pattern of Category -1 Failure pulmonary tuberculosis patients

S. No	DRUG	Resistance	Sensitivity	Percentage (%)
1	Rifampicin	20	13	60%
2	Isoniazid	25	8	75%
3	Ethambutol	20	13	60%
4	Pyrazinamide	24	9	72%
5	Streptomycin	21	12	63%
6	Ofloxacin	19	13	57%
7	Kanamycin	4	29	12%
8	Amikacin	2	31	6%
9	Capreomycin	2	31	6%

Figure I: Failure



DST IN CAT-I RELAPSE GROUP

Among 55 Patients, 33 have taken DOTS treatment and 22 have taken Non-DOTS treatment. 25 (45%) were resistant to Rifampacin (RIF), 28 (50%) to Isoniazid (INH), 13 (23%) to Ethambutol (EMB), 26 (47%) to Pyrazinamide (PZA), 13 (23%) to streptomycin (SM), 13 (23%)

to quinolones (Q) and in the second line inject able Aminoglycosides , 3(5.5%) were resistant to kanamycin(Km), 2(3.6%) to amikacin(Amk) and 4 (7.3%) were resistant to capreomycin(Cm) 4(7%) cases were XDR-TB, 20 (36%) were MDR-TB, 3(5%) was Monoresistant, 3(5%) were Polyresistant and 25(45%) were sensitive to all drugs.

Table II: DST Pattern of Category-1 Relapse Pulmonary Tuberculosis Patients

S.No.	DRUG	RESIS	SENS	(%)
1	Rifampicin	25	30	45%
2	Isoniazid	28	27	50%
3	Ethambutol	13	42	23%
4	Pyrazinamide	26	29	47%
5	Streptomycin	13	42	23%
6	Ofloxacin	13	42	23%
7	Kanamycin	3	52	6%
8	Amikacin	2	53	4%
9	Capreomycin	4	51	7%

FigureII: Relapse

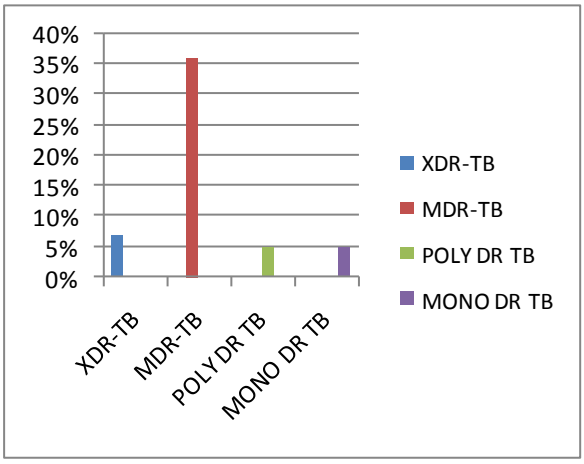


Table III: Comparison of Drug Resistance in Cat- I Failure and Cat- I Relapse Groups

S. No	Drug	Cat-I Failure	Cat-I Relapse
1	R	60%	45
2	H	75	50
3	E	60	23
4	Z	72	47
5	S	63	23
6	Q	57	23
7	Km	12	6

8	Amk	6	4
9	Cm	6	7

Table IV: Highest Individual Drug Resistance in Both Groups (for first line drugs)

Highest individual drug resistance in CAT-I Failure group	**Highest individual drug resistance in CAT-I Relapse group**
INH 75%	INH 50%
PZA 72%	PZA 47%
SM 63%	R 45%
R 60%	E 23%
E 60%	SM 23%

DOTS Patients Vs Non-DOTS Patients:

Fifty two percent of the patients (46/88) in this study received the DOTS category-1 regimen i.e. 13 in Cat-1 failure group while 33 in Cat-1 relapse group. Forty eight percent (42/88) patients were not registered under DOTS program i.e. 20 patients in Cat-1 failure group while 22 patients in Cat-1 Relapse group.

DOTS/Non-DOTS Total Patients	**Cat 1 Failure**	**Cat 1 Relapse**	**Total**	**%**
DOTS	13	33	46	52
Non-DOTS	20	22	42	48
Total	33	55	88	

Chi Square test was applied for both categories of dots treatment and non dots treatment comparison and it was statistically significant (p= 0.001)

While fifty percent of the total patients population in this study i.e. 44/88 (20 in Cat-1 failure and 24 in Cat-1 Relapse) were found to be suffering from MDR/XDR-TB, more drug resistance was seen among patients who belonged to non – DOTS group. Among 46 Patients who were treated under DOTS program, Forty three percent i.e. 20/46 (7 in Cat 1 failure, 13 in Cat 1 relapse) were found to be suffering from MDR/XDR-TB, while a higher number i.e. fifty seven percent of unregistered (Non-DOTS) patients, 24/42 (13 in Cat 1 failure, 11 in Cat 1 Relapse)

were found to be having MDR/XDR-TB. The difference was statistically significant with a chi square P value = 0.0002.

DOTS/Non DOTS MDR/XDR Patients	Cat 1 Failure with MDR/XDR-TB	Cat 1 Relapse with MDR/XDR-TB	Total	%
DOTS	7	13	20	43
Non-DOTS	13	11	24	57
Total	20	24	44	

DISCUSSION:

MDR-TB is the most serious emerging challenge which is even more serious in developing countries like Pakistan. In the coming years it is likely to play havoc worldwide. If left unchecked, it has a potential to bring back the pretreatment era. DR-TB poses a continuous threat for the global control efforts for TB. According to WHO Global TB report 2011, prevalence of MDR-TB in new TB cases is 3.4% and in retreated cases it is 21%. Pakistan stands 4th among 27 high burden MDR-TB countries. A study from Pakistan in 2008 showed 1.8 % primary MDR – TB.[18] The current situation seems to be more complex. Factors like unknown drug quality, poor availability of drugs, inadequate regimens and follow up, lack of health education, poverty, malnutrition, immune compromised states like drug addiction and HIV, improper DOTS implementation and lack of political commitment have all contributed in the progression of DR-TB.[19]

WHO / IUATLD designed the patient's categories (I-IV), in order to standardize the management of TB especially for developing world. Unfortunately it seems as if there is some inadequacy in the design of these categories especially the cat II regimen for cat-1 failure or relapse patients. Worldwide, though few studies are available, yet they all emphasize the need for DST to rule out DR-TB before starting the retreatment after taking cat I ATT as there is evidence of unacceptable high level of DR-TB in this group. A study from Peru clearly revealed that a large proportion (three- quarter) of cat I failure patients with DST have MDR-TB.[9] Another study from Siberian prison in 1999 depicts 35% of treatment failure rate of cat II for cat I failure patients despite implementation of strict DOTS programme.[14] Studies from Lima (Peru) and Tehran (Iran) showed that treatment success of cat-I failure according to DST was quite high as compared to conventional cat II regimen only.[16-17] In a similar study published in British Medical Bulletin in 2005, the outcome of patients was significantly worse in WHO retreatment regimen in spite of DOTS -Plus strategy.[20] Another study from Vietnam depicts that 80% of category-I failure had MDR as compared to category-I relapse which showed only 8% MDR-TB.[15]

These studies clearly raise a warning call to reconsider the re-treatment regimens in order to combat the emerging epidemic of DR-TB and its associated morbidity and mortality.

In our study Cat-1 failure and relapse cases were studied for drug resistant tuberculosis (DR-TB) in order to assess the situation in this part of the world. DR-TB was found in 67% (59/88) of

the total cases while 50% of total patients (44/88) were found to be suffering from MDR/XDR-TB. In the cat-1 failure cases MDR/XDR -TB was 60 %, while in cat-1 relapse cases it was 43%**.** The results of this study are almost identical as shown by the studies already mentioned. The percentage of MDR/XDR -TB in cat-1 failure cases is higher than that in relapse cases (60% vs. 43% respectively), though the difference was not statistically significant. Alarmingly, among the small total number of patients included in this study, XDR-TB was detected in 8 patients (4 patients in cat-I failure group and 4 patients in cat-I relapse group) including 3/8 patients who were found to be suffering from total drug resistance (TDR).

Fourty two patients (48%) in our study were treated in a non-DOTS program, mainly by private practitioners. 20/33 non-DOTS in Cat-1 failure and 22/55 in cat-1 relapse could be the important reason for the development of more MDR/XDR- TB (57%) in these patients as compared to (43%) MDR/XDR- TB in DOTS treated group. This is especially true in category-I failure group where 13/20 patients with MDR/XDR-TB were found to be unregistered with the DOTS program for their Anti-TB treatment as compared to 7/20 patients with MDR/XDR-TB which were under DOTS program. This highlights the importance of proper implementation of DOTS strategies which can help preventing the progress of MDR/XDR-TB.

Interestingly, in the category-I relapse group; the MDR/XDR-TB was higher in the patients who were treated under DOTS program i.e. 13/24 patients as compared to those patients who were not treated under DOTS program i.e. 11/24 patients. These points out the need to re-evaluate the DOTS program in order to curtail its deficiencies especially by strengthening its supervision. This also invites further studies to reconsider the WHO category-1 treatment which recommends the use of two drugs i.e. Isoniazid plus Ethambutol (HE) in the continuation phase.

Another interesting finding of the present study is the identification of PZA as the second most resistant drug in both groups after INH. PZA is still considered as the least resistant of all the available first line anti TB drugs. WHO/NTCP guidelines still advocate its use in the treatment of MDR-TB even if DST is not available. This recommendation needs further evaluation.

Though the total number of patients in our study was small (33 in cat-1 failure and 55 in cat-1 relapse), yet considering the overall high percentage of MDR/XDR –TB, recommendation for diagnosis and treatment needs further multi centre studies involving larger number of patients.

CONCLUSION:

In the absence of well designed scientific evidence, our study is an effort to evaluate some of the basic issues involving the decision making for TB patients in cat-1 failure and relapse. This study shows unacceptably high prevalence of MDR/XDR-TB in both Category –I failure and relapse patients. Therefore, it seems necessary to carry out DST before the re-treatment of such patients in order to avoid unacceptable delays in the diagnosis of a significant number of patients in this category who already possess MDR/XDR-TB. This will prevent the spread of MDR/XDR-TB and its associated morbidity and mortality by choosing the correct regimen on the basis of DST results performed in the beginning.

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